IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PACIFIC BIOSCIENCES OF CALIFORNIA, INC.,	)	
Plaintiff,	)	C.A. No. 17-cv-275-LPS C.A. No. 17-cv-1353-LPS
v.	)	
OXFORD NANOPORE TECHNOLOGIES, INC.,	)	**JURY TRIAL DEMANDED**
Defendant.	)	

PLAINTIFF'S OPENING CLAIM CONSTRUCTION BRIEF

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I. INTRODUCTION

This claim construction proceeding is directed to four patents that disclose and claim techniques that greatly increase the accuracy and effectiveness of nanopore-based polynucleotide sequencing. As explained in PacBio's tutorial, these techniques were a breakaway from the approaches researchers had spent years exploring in an attempt to develop a viable nanopore sequencing technique, and have helped to unlock the potential of nanopore sequencing.

While the technology underlying the inventions can be complex, the instant claim construction disputes are straightforward. As documented herein, PacBio's constructions focus on the claims themselves, which necessarily form the "starting point for any claim construction…." *TomTom, Inc. v. Adolph,* 790 F.3d 1315, 1328 (Fed. Cir. 2015). And, as the Federal Circuit has repeatedly noted, "[c]laim terms are generally given their plain and ordinary meanings to one of skill in the art when read in the context of the specification and prosecution history…" *Id*. ONT, in contrast, seeks to redraft the claims to change their scope and substitute its preferred language. ONT's constructions ignore express definitions set forth in the specification, attempt to read limitations from embodiments into the claims, and read out claimed embodiments from the independent claims. At odds with so many core claim construction principles, ONT's constructions should not be adopted.

II. ARGUMENT

A. '929 Patent

1. Polynucleotide

Claim Term/Phrase	Plaintiff's Construction	Defendant's Construction
"[a / the] polynucleotide" (claim 1)	A molecule having multiple nucleotides	A double-stranded nucleic acid molecule comprising a first terminal portion, an intermediate portion, and a

		second terminal portion wherein at least a first linker ligated to the first terminal portion of the nucleic acid molecule connects a 3' terminus at the first terminal portion with a 5' terminus at the first terminal portion

The parties dispute whether the term "polynucleotide" should be given its ordinary meaning (PacBio's position), or whether limitations from one particular embodiment should be imported into the claims (ONT's position).

Polynucleotide is a straightforward term, easily understood by a layperson. It is commonly known that the prefix "poly-" means "multiple" or "many." PacBio's construction simply applies this commonly understood meaning to the term "nucleotide." This plain meaning is confirmed by the specification of the '929 Patent. For example, the '929 Patent provides examples of a "polynucleotide molecule" as "e.g. DNA, RNA, etc." D.I. 80-6 at 77:22-23. DNA and RNA molecules are a sequence or chain of nucleotides (*i.e.,* a molecule having multiple nucleotides), which may be single-stranded or double-stranded. Moreover, this plain meaning is consistent with how the term would be understood by a person of ordinary skill in the art. *See, e.g.*, Ex. 1 [McGraw Hill Scientific Dictionary] ("A linear sequence of nucleotides"); Ex. 2 [Dictionary.com] ("a sequence of nucleotides, as in DNA or RNA, bound into a chain").

In contrast, ONT's construction includes a myriad of peculiar limitations that are not remotely invoked by the general term "polynucleotide:"

- a "first terminal portion"
- an "intermediate portion"
- a "second terminal portion"
- a "linker" that is "ligated" and connects the "3' terminus at the first terminal portion with a 5' terminus at the first terminal" portion

ONT seemingly plucks this language from a single embodiment appearing in column 10 of the '929 Patent that pertains to "paired-end sequencing." *See* D.I. 80-6 at 10:29-38. As the specification explains, in paired-end sequencing, one sequences the ends, but not the middle, of the template molecule. *See id.* a 10:41-45 ("The template molecule is subjected to a sequencing process in which sequence reads are generated for the first terminal portion and the second terminal portion, but sequence reads are not generated for the intermediate portion...."). Hence, in paired-end sequencing, an "intermediate" portion of a molecule is sandwiched by "terminal" portions.

Yet, while nanopore sequencing can potentially be used to perform paired-end sequencing, nothing in the intrinsic record suggests that claims should be limited to such an approach. There is no disavowal or disclaimer anywhere in the intrinsic record. Quite the contrary, the '929 Patent unambiguously states that the cited embodiment encompasses only "certain aspects" of the claimed invention. *Id.* at 10:27-29 ("***In certain aspects***, the invention provides…").[1] Moreover, the '929 Patent discloses embodiments that do not perform paired-end sequencing. *Id.* at 37:66-38:11 (sequencing the entire complementary strands 202 and 204); Figs. 21(A), 21(B). ONT's attempt to import limitations from one embodiment into the definition of "polynucleotide" is "one of the cardinal sins of patent law." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1320 (Fed. Cir. 2005). As this Court and the Federal Circuit have ruled, claims are not to be construed to "improperly limit the scope of the claims to a preferred embodiment." *Galderma Labs. Inc. et. al., v. Amneal Pharm., LLC et. al.*, No. 11-cv-1106-LPS, 2013 WL 3942965 at *5 (D. Del., Jul. 30, 2013).

ONT's proposal to include a "linker" requirement in the definition of "polynucleotide" is not just another attempt to improperly import the embodiment at column 10 into the claims, but is

[1] All emphasis added unless otherwise noted.

directly inconsistent with the claim language. Indeed, where the patentees wished to include a "linker" limitation in the claims, they did so. Dependent claim 8 recites a polynucleotide that is "linked," giving rise to the presumption that claim 1 encompasses ***unlinked*** polynucleotides. D.I. 80-6 at Claim 8. Likewise, dependent claim 10 recites linked polynucleotides that are "linked by a linker comprising a nucleotide." *Id.* at Claim 10. The parties agree that this refers to a "nucleic acid covalently bonding a 3'end of the first nucleic acid segment with a 5' end of the second nucleic acid segment." *See* D.I. 80-1. ONT's construction would thus improperly give Claims 1, 8, and 10 co-extensive scopes, rendering the dependent claims redundant. *See Liebel–Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 910 (Fed. Cir. 2004) ("[W]here the limitation that is sought to be 'read into' an independent claim already appears in a dependent claim, the doctrine of claim differentiation is at its strongest.").

2. Monitoring Variations In Ionic Current

Claim Term/Phrase	Plaintiff's Construction	Defendant's Construction
"monitoring variations in ionic current" (claim 1)	No Construction Necessary	Intermittently monitoring variations in ionic current

The parties dispute whether the term "monitoring variations in ionic current" requires construction. PacBio believes that the claim terms are ordinary English words that require no construction. ONT's proposed construction merely adds the word "intermittently" without actually construing any words in the term.

"Monitoring" is an easily understood English word that does not need construction. There is no indication in the claim or the specification that the word "monitor" has been given any special meaning. *See* D.I. 80-6 at 77:19-22. "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim

construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Phillips,* 415 F.3d at 1314. And this court has followed that reasoning, ruling that claims need not be construed when the limitation is "sufficiently understandable for a jury." *Intel Corp. v. Future Link Systems, LLC,* No. 1-14-cv-00377-LPS, 2016 WL 4162648 at *3 (D. Del., Aug. 2, 2016); *see also Walker Digital, LLC, v. Google, Inc*., No. 11-cv-00318-LPS, 2013 WL 3876002 at *5 (D. Del., Jul. 25, 2013) (no construction necessary because the meaning of the claim term "will be made clear to the jury from the overall claim language, the construction of other terms, and the parties' experts' testimony…").

ONT's construction does not define any of the terms. Instead it merely repeats them and adds the limitation "intermittently." ONT's construction serves only to limit the claims to a specific type of "monitoring." ONT's introduction of "intermittently" is inconsistent with the use of "monitoring" in the specification. The '929 Patent uses the term "intermittent" when describing a specific embodiment of a "detection" process. *See, e.g*., *id.* at 77:12-14; 77:43-49. Notably, however, the '929 Patent never uses "intermittent" to describe "monitoring."

ONT again seemingly seeks to limit the claims to "paired-end" read processes in which there are "intermediate portions" of the molecule that are not subject to sequencing, such that the detection is "intermittent." *See* D.I. 80-6 at 10:41-45. As documented above, there is no disavowal or disclaimer in the intrinsic record that would justify such a limitation. *See Hill-Rom Serv. v. Stryker Corp.,* 755 F.3d 1367, 1372 (Fed. Cir. 2014) (limitations should only be read into the claim when "the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction." (internal quotation marks and citation omitted).

3. Redundant Sequence Information

Claim Term/Phrase	Plaintiff's Construction	Defendant's Construction
"redundant sequence information" ('929 Patent)	No Construction Necessary	Information that includes the identity and order of each of the bases of the complementary strands

The parties' dispute whether the term "redundant sequence information" requires independent construction. No such construction is required because the content of the "redundant sequence information" is described in the claim itself. Specifically, claim 1 recites "redundant sequence information [that] ***comprises the nucleotide sequence of the complementary strands***." D.I. 80-6 at Claim 1.

ONT's proposed construction merely combines its construction for "nucleotide sequence," which is discussed below in Part II(D)(1), with the description of "redundant sequence information" that is already present in Claim 1. The inappropriateness of ONT's proposed construction for "redundant sequence information" is confirmed by inserting it into the claim along with ONT's construction for "nucleotide sequence." Shown below is the result of this exercise, with ONT's construction for "redundant sequence information" shown in red and ONT's construction for "nucleotide sequence" shown in green:

> wherein the ***information that includes the identity and order of each of the bases of the complementary strands*** comprises ***the identity and order of each of the bases*** of the complementary strands

As the foregoing shows, ONT's construction adds nothing and only serves to repeat language that is already present in the claim. Such a construction should not be adopted. *See, e.g.*, *Apple, Inc. v. Ameranth, Inc.*, 842 F.3d 1229, 1237 (Fed. Cir. 2016) ("The Board was correct to not include in its construction of 'menu' features of menus that are expressly recited in the claims. Ideally, claim

constructions give meaning to all of a claim's terms….Construing a claim term to include features of that term already recited in the claims would make those expressly recited features redundant."); *U.S. Surgical Corp., v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997) (emphasizing that the claim construction process should not devolve into an "exercise in redundancy").

4. Determining A Consensus Sequence For The Region Of Interest

Claim Term/Phrase	Plaintiff's Construction	Defendant's Construction
"determining a consensus sequence for the region of interest" (claim 1)	Determining the most likely actual nucleotide sequence for the region of interest	Determining a sequence of nucleotides compiled by inserting the nucleotide occurring most often at each position in the real sequences for the region of interest

The parties' dispute is over the construction of "consensus sequence." PacBio's construction is taken directly from the specification and is consistent with the method of the claim. ONT's construction is a partial excerpt of a secondary definition for "consensus sequence" found in an online dictionary.

PacBio's construction is consistent with the specification and Claim 1. The '929 Patent explains that a single sequence is prone to errors because there are no methods to check any discrepancies. *See* D.I. 80-6 at 61:38-52. The specification further states that one of the claimed inventions is directed to "machine-implemented methods for transforming nucleotide sequence read data into consensus sequence data" where "***consensus sequence data is*** representative of a ***most likely actual sequence*** of the template nucleic acid." *Id.* at 12:6-12. Claim 1 of the '929 Patent describes a method of using complementary strands of the same template, which contain redundant sequence information. *Id.* at Claim 1. By comparing the nucleotide sequence of the redundant sequence information, the method of claim 1 allows for determining the most likely

actual nucleotide sequence.

ONT's construction has no basis in the specification or the claims, and is an incomplete excerpt of a dictionary. ONT's construction is taken from the second definition of an online dictionary webpage.[2] ONT construction omits, however, the majority of the definition. The full definition is "a sequence of nucleotides or amino acids that is used to describe ***a number of related but not identical sequences***. It is compiled by inserting the nucleotide occurring most often at each position in the real sequences." Ex. 3 [Online Medical Dictionary].

Limiting the claims to this definition is unjustified by the claim language and inconsistent with the specification. The '929 Patent includes embodiments that determine the consensus sequence not through inserting nucleotides, but by using a "directed graph." *See* D.I. 80-6 at 12:6-47. In this embodiment, a directed graph is constructed "wherein a given weight for a given edge [of the graph] represents the log-likelihood that a given pair of nodes… is truly a reconstruction of the template nucleic acid." *Id.* at 12:25-28. ONT's construction is improper, as it would read this embodiment out of the claims. *See Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1320 (Fed. Cir. 2005) ("A claim construction that does not encompass a disclosed embodiment is...rarely, if ever, correct." (alteration in original) (internal quotation marks and citation omitted)).

ONT's construction also does not make sense in the context of Claim 1, which encompasses comparing only ***two*** complementary strands of nucleic acids (redundant sequence information), and determining a consensus sequence from those two strands. ONT's construction requires "inserting the nucleotide occurring ***most often*** at each position." It is impossible to

[2] The webpage was identified in an IDS during the prosecution of the '929 Patent. The prosecution history is silent, however, on which definition on that webpage was considered relevant.

determine which nucleotide occurs most often when there are only two possible strands to compare. ONT's construction would render a covered implementation of claim 1 nonsensical.

5. Linked

Claim Term/Phrase	Plaintiff's Construction	Defendant's Construction
"linked" (claim 8)	No Construction Necessary	Covalently bonded at the 3′ end of the first nucleic acid segment and the 5′ end of the second nucleic acid segment

The parties dispute whether the word "linked" requires construction. ONT seeks to import the limitations of dependent claim 10 into claim 8. Ultimately, this is the same tactic ONT has attempted with the construction of "polynucleotide." *See supra* Part II(A)(1).

The '929 Patent does not set forth any specialized definition for, or disclaimer of, "linked." As "linked" is an ordinary English word, and would be readily understood, it does not require construction. *See Phillips*, 415 at 1314; *see also Intel*, 2016 WL 4162648 at *3 (no construction necessary when terms are "sufficiently understandable for a jury"); *Walker Digital*, 2013 WL 3876002 at *5.

ONT's construction seeks to import limitations from an embodiment—limitations that are already the subject of dependent claim 10. Claim 10 recites "[t]he method of claim 8, wherein the complementary strands are linked by a linker comprising a nucleotide." D.I. 80-6 at Claim 10. As noted above, the parties agree that a "linker" is a "nucleic acid covalently bonding a 3' end of the first nucleic acid segment with a 5' end of the second nucleic acid segment." *See* D.I. 80-1. Thus, ONT's proposed construction would improperly render claim 10 superfluous. *Phillips*, 415 F.3d at 1315 ("The presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim."); *see also*

Galderma, 2013 WL 3942965 at *5 (claim construed as ordinary meaning when defendant's construction would "improperly limit the scope of the claims to a preferred embodiment.").

B. '400 and '323 Patents

There is substantial overlap in the terms proposed for construction from the '400 and '323 Patents, and so the terms for both patents are addressed together. Any relevant differences are addressed on a term-by-term basis.

1. N

Claim Term/Phrase	Plaintiff's Construction	Defendant's Construction
"N" ('400 Patent claim 1 and '323 Patent claim 1)	An integer	The number of bases that affect the current measurement

The dispute between the parties is whether it is sufficient to define "N" as an integer (PacBio's position), or whether "N" must be further defined in terms of the permissible values it can take on (ONT's position). In particular, ONT seeks to limit "N" to the number of bases that "affect the current measurement." ONT's definition, is not just inconsistent with the claims, but unwarranted because the claim language already defines the permissible values for "N."

The independent claims explain that "N" characterizes a number of "monomeric ***units***." *See* D.I. 80-3, D.I. 80-4 at Claim 1. This context alone establishes that "N" is an integer. *Phillips*, 415 F.3d at 1314 ("[T]he context in which a term is used in the asserted claim can be highly instructive [in claim construction]."). There is no genuine dispute that "N" is only an integer, as opposed to a real or decimal number. Indeed, the variable "N" is commonly used in math and science to denote an integer. *See* Ex. 4 [Wikipedia page for Variable_(mathematics)] ("n usually denotes a fixed integer, such as a count of objects or the degree of an equation.").

The parties' dispute is about the values "N" can take on. The claims already define these

permissible values. In particular, "N" is "three or greater" and is the number of "monomeric units" that are "in the pore" for which the signal "varies." *See* D.I. 80-3, D.I. 80-4 at Claim 1 ("measuring an electrical signal which ***has a value that varies for at least N monomeric units*** of the template nucleic acid in the nanopore…"). Thus, as the claims make clear, the permissible values of "N" are those that are "three or greater" and represent a number of units "in the pore" for which the signal "varies." No further limitation on the permissible values of "N" is appropriate.

Yet, ONT seeks to limit "N" to the total number of nucleotides that "affect the current measurement." This is directly at odds with the claim language, which refers to no such thing, but instead simply refers to "a property which has a value that varies for N monomeric units of the template nucleic acid in the pore." The claim language is thus broader than ONT's proposed construction. Consider, for example, a situation where there are four total nucleotides in the pore, and all four "affect the current." In such cases, the current will almost certainly vary not just for the four total units in the pore, but also for a subset of just three nucleotides. Indeed, it could be that three of the nucleotides are responsible for the overwhelming bulk of the signal, while the fourth makes a slight contribution. ONT, however, would limit the claims only to approaches that use every single nucleotide that "affects the current measurement," regardless of whether such approaches are unnecessary or infeasible.

There is no disavowal or disclaimer in the intrinsic record to justify this extreme limitation. ONT's proposed construction seemingly comes from a description of "Base Calling Methods" in the specification, and is not a definition. *See* D.I. 80-3 at 39:48-62. This description does not remotely purport to define "N" for the purposes of the claims, but simply uses "N" as a variable to explain the total possible number of current levels. *Id.* at 39:55-60. Likewise, ONT cites a portion of the file history that describes an "example" where all nucleotides that "affect" the measurement

are used. *See* Ex. G. But nothing in the file history disavows other embodiments. Moreover, the cited portions of the file history pertain to distinguishing prior art on a ground that has nothing to do with the meaning of "N." ONT's reliance on the file history is thus entitled to no weight. *See, e.g.*, *Inline Plastics Corp. v. EasyPak, LLC*, 799 F.3d 1364, 1370 (Fed. Cir. 2015) ("The distinction between Urciuoli and the ′003 device has no relation to the number of score lines on a tear strip, but rather to differences in the structure and opening mechanism as a whole.").

2. "Calibration Information" Terms

Claim Term/Phrase	Plaintiff's Construction	Defendant's Construction
"calibration information **produced by measuring such property** for 4 to the N sequence combinations" ('400 Patent claim 1) "calibration information **that accounts for the electrical signal** for 4 to the N sequence combinations" ('323 Patent claim 1)	No Construction Necessary	Calibration information generated by measuring the property for each of the 4^N possible combinations of nucleotides

The parties dispute whether the phrases "that accounts for the electrical signal" ('323 Patent) and "produced by measuring such property" ('400 Patent) should be replaced with "generated by measuring the property" as proposed by ONT.

None of the words of the relevant phrases (nor the phrases themselves) are terms of art. The terms "accounts for," "electrical signal," and "produced" are all easily understood English words that need no construction. There is nothing in the claims or specification to suggest that these phrases need any particular definition. *See generally* D.I. 80-3, D.I. 80-4. These terms should thus be given their plain and ordinary meaning. *See Phillips,* 415 F.3d at 1314; *see also Intel*, 2016 WL 4162648 at *3; *Walker Digital*, 2013 WL 3876002 at *5; *Plastic Omnium Adv.*

Innov. And Research v. Donghee Am., Inc., No. 1-16-cv-00187-LPS, D.I. 325 at 4-7 (D. Del. May 31, 2018) (no construction necessary for "molten plastic") (Ex. 5).

ONT seeks to redraft the claims to substitute its preferred phrase "generated by measuring" into the claims. ONT's proposed language has no basis in the intrinsic evidence, and provides no clarity for potential jurors. ONT's proposed constructions should be rejected.

In the context of the '400 Patent, ONT seeks to substitute the word "generated" for "produced." ONT's proposed construction does not address any actual dispute as to claim scope, but rather simply substitutes its preferred language. A comparison of the ordinary meaning of "produce"—to cause to have existence—with that of "generate"—to bring into existence—yields no clarity. *Compare* Ex. 6 (M-W definition of produce) *with* Ex. 7 (M-W definition of generate). There is no basis for this redrafting of the claims. *See Chef Am., Inc. v. Lamb-Weston, Inc*., 358 F.3d 1371, 1373 (Fed. Cir. 2004) ("Courts are not permitted to redraft claims.").

The patentees were clear in their use of "produced" versus "generate." The '400 Patent only uses "produce" in connection with calibration information (*see, e.g.*, D.I. 80-3 at 41:31-35), and it uses "generate" in connection with "event data" (*see e.g.,* D.I. 80-3 at 39:41-42). There is no justification for ONT's proposed substitution of "generated" for "produced" in light of the Patentee's clear choice of language. *See Trustees of Columbia Univ. in City of New York v. Symantec Corp*., 811 F.3d 1359, 1366 (Fed. Cir. 2016) ("the construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction" (internal quotations omitted)).

In the context of the '323 Patent, ONT's proposed construction would do violence to the claim language, and read claimed embodiments out of independent claim 1. ONT's proposed construction would remove from the claims the phrase, "that accounts for the electrical signal,"

and substitute in its place, "generated by measuring the property." First, ONT's proposed construction would introduce ambiguity and potentially confuse jurors. Substituting ONT's construction into the claim language causes it to read "performing a process including comparing the electrical signal from step (c) to calibration information generated by measuring the property for each of the 4^N possible combinations of nucleotides." Adopting ONT's construction would simply confuse the jurors as to which "property" is supposed to be measured. This runs counter to the whole purpose of claim construction. *Embrex, Inc. v. Service Eng'g Corp.*, 216 F.3d 1343, 1347 (Fed. Cir. 2000) (claim construction is meant to "understand and explain, but not to change, the scope of the claims").

Second, ONT's proposed construction would read claimed embodiments out of the only independent claim of the '323 Patent. Unlike the '400 Patent, the claims of the '323 Patent are directed to calibration information "that accounts for the electrical signal." D.I. 80-4 at Claim 1. Dependent claim 6 further recites that the calibration information "is determined experimentally." *Id.* at Claim 6. In contrast, dependent claim 7 recites that "at least some of the calibration information … is calculated." *Id.* at Claim 7. Thus, the calibration information of claim 1 must be broad enough to include calibration information that is determined experimentally—whether measured directly or by other means—and at least some calibration information that is calculated—whether based on measurements or another criterion.

This scope is reflected in the intrinsic evidence. In one embodiment directed to "single-molecule nanopore sequencing based on exo-nuclease release," the calibration information includes "previously calibrated experiments and determination of the probability distributions" of the "nucleotide-identity." *Id.* at 41:46-63. In other words, the calibration information includes both measured experimental properties and calculated probability distributions. *See id.* This is

further reflected in the prosecution history, where the Examiner discussed the calibration information by identifying both measured and calculated values. D.I. 80-18 at 3-5. In the response (in which the Patentee overcame the prior art), the Patentee consistently referred to "calibration information ***that accounts for*** the electrical signal" in analyzing the claims. D.I. 80-8 at 6 (emphasis added).

ONT's proposed construction—generated by measuring—is improper. For the '400 Patent, ONT's proposed construction does not resolve any dispute as to the claim scope and would improperly substitute ONT's preferred word for the Patentee's. *See Trustees of Columbia Univ.*, 811 F.3d at 1362 ("We begin a claim construction analysis by considering the language of the claims themselves."). For the '323 Patent, ONT's proposal does not capture the full claim scope of the claims and cannot be correct. *Medrad, Inc.*, 401 F.3d at 1320 ("A claim construction that does not encompass a disclosed embodiment is ... rarely, if ever, correct." (alteration in original) (internal quotation marks and citation omitted)).

3. In The Nanopore / In The Pore

Claim Term/Phrase	Plaintiff's Construction	Defendant's Construction
"in the pore" ('400 Patent claim 1) "in the nanopore" ('323 Patent claim 1)	No Construction Necessary	Between the entrance and exit of the nanopore

The parties dispute whether the word "in" requires construction. "In" does not require construction, as a layperson would readily understand the term. Just as a juror would understand that a person with her legs and feet in a pool was "in" the pool, a juror would understand that a polynucleotide that has any number of bases in a nanopore is "in the nanopore."

In contrast, ONT proposes that this Court construe the well-understood preposition "in" to

mean "between the entrance and exit of." ONT seeks to draw an artificial box around the nanopore and construe "in" to require that the polynucleotide is located entirely within that box. Yet again, ONT proposes a construction of a basic and clear English word by adding unnatural limitations. Not only is "in" already an easily understood word, ONT's construction introduces ambiguity. ONT's construction provides no guidance as to whether a polynucleotide that completely fills the space between the "entrance" and "exit" of the pore but is also partly outside that space is "in the pore," or whether the molecule must fill up the entire space between the "entrance" and "exit" to be deemed "between" them. As the word "in" is already sufficiently clear, and because the proposed construction does nothing to clarify it, no construction is necessary. *See, e.g.*, *Intel*, 2016 WL 4162648 at *3.

C. '056 Patent

1. Kinetic Step

Claim Term/Phrase	Plaintiff's Construction	Defendant's Construction
"kinetic step" (claim 1)	Not Indefinite/A reaction step that can be associated with a rate constant	Indefinite

ONT argues that the term "kinetic step"—a term that both parties agree is discussed across 14 columns and illustrated in Figures 32 and 33 of the '056 Patent (*see* D.I. 80-2 at 11)—is indefinite. To the contrary, kinetic step is well defined in the intrinsic evidence and would be readily understood by a person of ordinary skill in the art as well as jurors.

A patent claim is indefinite if, "viewed in light of the specification and prosecution history, [it fails to] inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014); *see also Ethicon Endo-Surgery, Inc. v. Covidien, Inc.*, 796 F.3d 1312, 1319 (Fed. Cir. 2015) (If "an

understanding of how to measure the claimed [feature] was within the scope of knowledge possessed by one of ordinary skill in the art, there is no requirement for the specification to identify a particular measurement technique.")

The specification of the '056 Patent explains in detail what a kinetic step is, and how to use the associated rate constants to graphically model chemical reactions. The detailed description of the claimed "kinetic steps" begins in column 24: "The present invention is generally directed to improved enzyme reaction compositions, methods, and systems that exhibit kinetic mechanisms having two or more slow, ***kinetically observable***, or partially rate-limiting ***reaction steps*** within an observable phase of the polymerase reaction." D.I. 80-5 at 24:33-37. "[E]ach step can be characterized as having a particular forward and reverse reaction rate that can be represented by a rate constant." *Id.* at 25:35-38. The '056 Patent describes exemplary kinetic steps, including: "incorporation," "enzyme isomerization," and "cofactor binding." *Id.* at 25:38-46; *see also* D.I. 80-20 at [0011]-[0014] (describing kinetic steps including "enzyme isomerization, nucleotide incorporation, and product release.").

Figure 32 is a representation of the incorporation biochemistry, including multiple kinetic steps (102, 104, 106, 108, 110, 112):

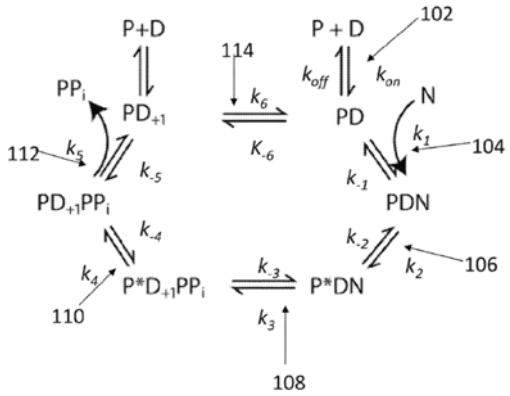

Figure 32

D.I. 80-5 at 25:35-26:18; *see also* 26:29-35 ("In some cases, the invention involves a process

having two or more kinetically observable steps that comprise steps after nucleotide binding through the step of product release. … In some cases, steps 108 (nucleotide incorporation) and 112 (product release) are the two slow, or kinetically observable steps.").

Each of these kinetic steps "may be characterized by the reaction constants" k_1-k_6, k_{on}, and k_{off}. *Id.* at 26:1-11. The '056 Patent provides "generally desirable… rate constants" for a variety of embodiments ranging from rate constants "that are lower than about 1000 per second" down to "lower than about 1 per second." *Id.* at 27:27-36. The specification also provides a number of exemplary ratios "of the rate constants of each [of] the two or more" kinetic steps. *Id.* at 27:44-50; 28:7-12.

The detailed description in the specification is consistent with the use of the term in the claims. Claim 1 is directed to a "translocating enzyme [that] exhibits two kinetic steps wherein each of the kinetic steps has a rate constant, and the ratio of the rate constants of the kinetic steps is from 10:1 to 1:10." *Id.* at Claim 1.

Given the detailed discussion of kinetic steps in the specification, the intrinsic evidence, and the claims of the '056 Patent, a person of ordinary skill in the art would understand the scope of the invention with reasonable certainty. To the extent any construction of the term "kinetic step" is necessary, a "reaction step that can be associated with a rate constant" is consistent with the express limitations of claim 1 and the intrinsic evidence.

D. '929, '400, and '323 Patents

1. "Sequence" Terms

Claim Term/Phrase	Plaintiff's Construction	Defendant's Construction
"nucleotide sequence" ('929 Patent claim 1)	Information reflecting the identity and order of each of the bases	The identity and order of each of the bases

"the sequence of the template nucleic acid" ('400 Patent claim 1; '323 Patent claim 1)	Information reflecting the identity and order of each of the bases of the template nucleic acid	The identity and order of each of the bases of the template nucleic acid

The parties agree that a nucleotide sequence contains information that indicates the identity and order of each of the bases in a polynucleotide. The dispute is how precise of an indication must be provided.

PacBio's construction further clarifies that a "sequence," as used in the specification, is information that does not necessarily consist of the precise identity and order of the bases. Rather, it is information that reflects the identity of the bases, with certain degrees of confidence. The '929 Patent identifies the possibility of error in a sequence, stating that nucleotide sequence reads "may not be identical to the actual sequence of the template nucleic acid molecule." D.I. 80-6 at 61:38-42. Furthermore, the '323 and '400 Patents disclose "nanopore sequencing" methods to decrease inaccuracies that result from single-molecule sequencing. *See e.g.*, D.I. 80-4 at 41:38-41, 41:52-63. They specifically disclose determining a "probability of nucleotide-identity for each metric," and adding "these probabilities… to obtain an overall probability of nucleotide-identity. *Id.* Each of these Patents discloses that the information generated by a nanopore sequence may not represent the real sequence of the template molecule with 100% accuracy. Thus, the nucleotide sequence obtained as a result of performing nanopore sequencing contains information reflecting the identity and order of the bases.

If ONT's construction of "nucleotide sequence" were adopted, a measured sequence that has an error would not be a "nucleotide sequence" because it was not identical to the actual sequence of the template nucleic acid. This cannot be correct.

E. All Patents

1. Nanopore

Claim Term/Phrase	Plaintiff's Construction	Defendant's Construction
"nanopore"	An opening sized so that the passage of a molecule through the opening can be detected by a change in a signal	A nanometer-sized hole

The term "nanopore" appears in all patents-in-suit. PacBio's construction is the verbatim definition provided in the Detailed Description of the Invention in the '400, '323, and '056 Patents.[3] The patents expressly define "nanopore" stating that, "***as used herein*** the term nanopore, nanometer scale aperture, and nanoscale aperture are used interchangeably [and]… refers to an opening which is of a size such that when molecules of interest pass through the opening, the passage of the molecules can be detected by a change in signal." D.I. 80-3 at 8:55-61; D.I. 80-5 at 8:55-61; D.I. 80-4 at 8:48-54. In situations when the specification offers "a special definition given to a claim term by the patentee…the inventor's lexicography governs." *See Phillips*, 415 F.3d at 1316.

ONT's construction comes from a single line in the Background of the Invention. Although the language cited by ONT gives a general description of a nanopore, it is not a clear definition. *See* D.I. 80-5 at 1:30-32 ("The concept of using nanometer-sized holes, or 'nanopores,' to characterize biological macromolecules and polymer molecules has recently been developed."). Nothing in the intrinsic record justifies deviating from the definition in the Detailed Description of the Invention, which is decisively introduced with the definitional phrase "as used herein."

[3] The '929 Patent provides a slightly different, but compatible definition. D.I. 80-6 at 77:14-16 ("A nanopore is a small pore in an electrically insulating membrane that can be used for single molecule detection.").

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Respectfully submitted,

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